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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/002,413	01/02/98	ALLEN	R 311772000500

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EXAMINER	
WILSON, M	
ART UNIT	PAPER NUMBER
1633	22

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/002,413	ALLEN ET AL.	
	Examiner	Art Unit	
	Michael Wilson	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-64* is/are pending in the application.

4a) Of the above claim(s) *3-10,13-16,18,19,21-26 and 29-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Applicant's arguments filed 4-4-00, paper number 18, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 3-10, 13-16, 18, 19, 21-26 and 29-32 have been canceled. Claims 33-64 have been added. Claims 33-64 are pending and under consideration in the instant application as they relate to a method of administering cells to create an immunologically privileged site as originally elected.

Claim Rejections - 35 USC § 112

1. Claims 37, 41, 59, 62 and 64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 37 and 59 are rejected because the genus of a second cell population that supplies an effective amount of "polypeptide growth factor, cytokine and polypeptide differentiation factor" is not disclosed as originally filed and is considered new matter. While the terms "growth factor", "cytokine" and "differentiation factor" are disclosed on page 8, line 31, the terms are used to describe nucleic acids. Claims 37 and 59 are not limited to transfected cells; therefore, the

scope of the claims regarding the genus of only "polypeptide" growth factors and differentiation factors was not contemplated as originally filed.

Claim 41 encompasses using the second cells attached to matrix while the RPE are not attached to the matrix which is not contemplated as originally filed and is considered new matter.

Claim 62 recites a second cell population of "insulin-producing cells" in the kit which was not contemplated as originally filed on page 4, lines 31-35 and is considered new matter.

Claim 64 recites the limitation of a "second population of cells" within the article of manufacture which is not disclosed in claim 23 as originally filed. Therefore, the scope of the article of manufacture with both RPE and the second cell population as claimed was not contemplated in the original disclosure and is considered new matter.

2. Claims 33-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transplanting retinal pigmented epithelial cells (RPE) and non-RPE using methods known in the art, does not reasonably provide enablement for administering RPE or RPE with non-RPE to obtain any therapeutic effect using any therapeutic protein/biologically active molecule in any disease as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The state of the art at the time of filing was such that RPE were known to provide an immune privileged site and that RPE could be transplanted to the retina to obtain a therapeutic

effect or to the brain to treat Parkinson's disease (Ye of record, 1993, Current Eye research, Vol. 12, pages 629-639, see page 629, column 1, line 1; page 630, column 2, line 24; last line of abstract and page 631, column 2, line 20; Cherksey, U.S. Patent 5,618,531, April 8, 1997, see the claims, especially claim 13; column 8, line 40; column 17, line 27; column 18, lines 25-44 and column 19, line 24). Goldstein of record teach administering neural cells such as RPE transfected with a vector encoding tyrosine hydroxylase to the brain to treat symptoms associated with Parkinson's disease (column 4, line 50; column 17, line 49; column 15, lines 27-60). It was also known that RPE may be co-administered with other cells (Goldstein et al., column 15, line 55; Cherksey, column 9, line 2) or encapsulated to prevent rejection (Goldstein, column 17, line 67).

In addition, various cells were able to be transplanted to produce therapeutic molecules. For example, Sigalla of record (Sept. 1, 1997, Human Gene Therapy, Vol. 8, pages 1625-1634) teach administering transfected pancreatic islet cells to the renal capsule and obtaining insulin release to therapeutic levels (page 1626, column 2, 2nd and 3rd paragraphs; page 1628, column 1, 4th paragraph and column 2, 4th and 5th full paragraphs). Weber of record (1997, J. Surg. Res., Vol. 69, pages 23-32) teach administering transfected pancreatic islet cells to the renal capsule and obtaining insulin release to therapeutic levels (page 25, column 1, "Islet transplantation"; page 27, paragraph bridging columns 1 and 2). Methods of encapsulating cells, such as Langerhans cells, to obtain an immunologically privileged site were well known in the art and were used to prevent rejection of transplanted cells (for example, Fraser of record, 1995, Cell Transplantation, Vol. 4, pages 529-534).

Therefore, the state of the art at the time of filing was such that RPE could be used to create an immunologically privileged site, that specific cells secreting specific therapeutic proteins could be used to treat specific diseases.

The specification contemplates treating a number of diseases (page 1, line 23; page 3, line 26; page 5, line 31), suggests genetically engineering RPE to produce any of a number of therapeutic proteins (page 8, line 31), and suggests delivering the RPE to any of a number of tissues (page 15, line 7). The specification also contemplates co-administration of RPE with cells supplying therapeutic molecules (page 4, line 20). Co-administration can be as a single composition or as separate compositions (page 4, line 23). Co-administration as defined in the specification encompasses administering RPE cells alone because RPE "supply therapeutic molecules" such as dopamine and because the definition does not require that the cells that "supply therapeutic molecules" are non-RPE. Cells that can be co-administered with RPE are neural cells, endocrine cells, muscle cells and other cells that produce a functionally active therapeutic molecule (sentence bridging pages 6 and 7). The specification demonstrates isolating and culturing fetal RPE *in vitro* (pages 16-20) obtaining FasL expression by RPE and apoptosis of thymocytes contacted with the RPE *in vitro* (pages 21-27). The specification does not provide any guidance or examples regarding administration of cells *in vivo*. Specifically, the specification does not provide any guidance on how to use pancreatic islet of Langerhans cells (claim 22). Therefore, the skill artisan is required to rely on what was known in the art regarding how to use

cells to treat disease responsive to a biologically active molecule or as pharmaceutical compositions.

Overall, the specification does not enable using any cell or combination of cells expressing any therapeutic molecule to treat any disease as broadly claimed. The specification and the knowledge in the art does not teach a reasonable representative number of embodiments of the claim to enable the breadth of the claims as written. For example, Langerhans cells (claim 63) can be used to treat diabetes upon transplantation and adequate secretion of insulin. The specification and the art do not support using Langerhans cells to treat any other disease or to secrete any other therapeutic molecule. It would require one of skill undue experimentation to determine any other method of using Langerhans cells other than to secrete insulin and ameliorate diabetes.

Specifically, the specification does not enable administering insulin-producing cells (claim 62), Langerhans cells (claim 63) or any other cells producing neurotransmitters (claims 34 and 55), hormones (claims 35 and 56), cytokine inhibitors (claims 36 and 57) or growth factors, cytokines, or differentiation factors (claims 37 and 58) to treat a neurological (claims 51 and 52), metabolic (claims 51 and 53), cardiac, endocrine, hepatic, pulmonary or immunological diseases (claim 51) as broadly claimed. Given the state of the art taken with the guidance provided in the specification, it would require one of skill undue experimentation to determine the parameters required to enable the numerous therapeutic embodiments of the claims other those specific methods that were known in the art at the time of filing. This rejection is based on how to use the methods or products claimed to treat disease.

The specification does not enable encoding biologically active molecules using a nucleic acid as broadly claimed (claims 39 and 40). Biologically active molecules such as aspirin are not proteins and cannot be encoded by nucleic acids. Therefore, such non-protein biologically active molecules are not enabled.

3. Claims 33-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 is indefinite because it is unclear whether applicants intend to administer RPE alone or RPE and non-RPE. The definition of co-administering is administration of RPE with cells supplying therapeutic molecules (page 4, line 20). It is unclear whether the definition intends to encompass administering RPE alone because RPE "supply therapeutic molecules" such as dopamine and because the definition does not require that the second cell population that "supply therapeutic molecules" are non-RPE. If two types of cells are being administered, it is unclear whether the cells are administered simultaneously. The specification states co-administration can be as a single composition or as separate compositions (page 4, line 23). It is unclear whether this is intended to mean administering two types of cells at the same time or at different times.

Claims 33-53 are indefinite because they are lacking an essential step in the method: the claims do not result in any treatment of disease or therapeutic effect.

Claims 39 and 40 are indefinite because the phrase a nucleic acid encoding said "biologically active molecule" is unclear. Some biologically active molecules such as aspirin cannot be encoded by a nucleic acid. It is unclear whether applicants intend to claim embodiments of encoding non-protein biologically active molecules using nucleic acids. Alteration of the term "biologically active molecule" to "biologically active protein" would overcome this rejection.

Claim Rejections - 35 USC § 102

4. Claims 33, 36-38, 44, 51-53, 54 and 57-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Ye of record (1993, Current Eye research, Vol. 12, pages 629-639) for reasons of record.

Ye teach treating retinal degeneration by administering $2.1x10^4$ allogeneic RPE to the retina of rabbits, obtaining immunologic privilege and an increase in the number of RPE cells in the retina (page 629, column 1, line 1; page 630, column 2, line 24; last line of abstract and page 631, column 2, line 20). RPE cells inherently secrete FasL, cytokine inhibitors and cytokines. Retinal degeneration is considered a neurological disease and a metabolic disease. The definition of co-administration of cells as defined in the specification encompasses RPE alone because RPE secrete therapeutic proteins and because neither the definition or the claim requires that the second population be non-RPE cells. Therefore, the definition in the specification encompasses

using RPE as both the RPE and second cell population. Thus, Ye anticipate all the limitations of the claims as written.

5. Claims 33-38, 41-45, 49, 51-61 and 64 are rejected under 35 U.S.C. 102(e) as being anticipated by Cherksey (Cherksey , U.S. Patent 5,618,531, April 8, 1997) for reasons of record.

Cherksey teach treating Parkinson's disease using 300-3.75x10^5 RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). RPE cells inherently secrete dopamine (column 8, line 40) which is a neurotransmitter (claim 34, 55), hormone (claim 35, 56) or chemokine (claim 38, 59) and FasL which is a cytokine inhibitor (claim 36, 57) and cytokine (claim 37, 58) and create an immunologically privileged site (claim 33). Parkinson's disease is considered both a neurological and metabolic disease (claims 52 and 53).

The definition in the specification encompasses using RPE as both the RPE and second cell population. The RPE are considered both the first and second cell populations. Cherksey specifically states allogeneic cells can be used for administration to a mammal (column 11, line 37). Therefore, Cherksey meets the limitation of the claims by administering allogeneic RPE which express dopamine and FasL.

Claim Rejections - 35 USC § 103

6. Claims 33-38, 41-49, 51-61 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cherksey (U.S. Patent 5,618,531, April 8, 1997) for reasons of record.

Because of the indefiniteness of the claims regarding whether administration of RPE alone is encompassed by the claims (see 112/2nd), claims 33-38, 42-45, 49, 51-61 and 64 are being rejected by Cherksey under both 102 and 103. Cherksey teach treating symptoms of Parkinson's disease using 300-3.75x10^5 RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24).

While Cherksey does not expressly teach administering RPE and a population of allogeneic non-RPE cells, Cherksey teaches transplanting a matrix having both RPE and glial cells attached to a host (column 9, line 2) and that the cells may be allogeneic to the host (column 11, line 37). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer RPE and glial cells wherein the glial cells are allogeneic as taught by Cherksey.

Cherksey does not expressly teach re-administering RPE or the second cell population (claims 46-48). However, it was common practice for the ordinary artisan at the time of filing to repeat treatments to obtain therapeutic effects. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to re-administer the RPE cells alone or the RPE/glial combination to sustain the therapeutic effects.

7. Claims 33, 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cherksey (Cherksey U.S. Patent 5,618,531, April 8, 1997) in view of Goldstein (Goldstein et al., U.S. Patent 5,300,436, April 5, 1994) for reasons of record.

Cherksey teach treating symptoms of Parkinson's disease using 300-3.75x10^5 RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). While Cherksey does not expressly teach administering RPE and a population of allogeneic non-RPE cells and such a limitation is not required in the claim (see 112/2nd), Cherksey teaches transplanting a matrix having both RPE and glial cells attached to a host (column 9, line 2) and that the cells may be allogeneic to the host (column 11, line 37). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer RPE and glial cells wherein the glial cells are allogeneic as taught by Cherksey. Cherksey does not teach transfecting cells with nucleic acids encoding a protein.

However, Goldstein teaches administering cells transfected with a vector encoding tyrosine hydroxylase to the brain to treat symptoms associated with Parkinson's disease (column 4, line 50; column 17, line 49).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of administering RPE or RPE and glial cells as taught by Cherksey and the method of treating Parkinson's using cells transfected with tyrosine hydroxylase as taught by Goldstein. Motivation is provided by Goldstein by stating RPE can be

transfected with tyrosine hydroxylase (column 15, lines 26-61, see line 59). Thus, it would have been obvious to one of skill in the art at the time of filing to transfect either the RPE or the glial cells with a vector encoding tyrosine hydroxylase to treat symptoms of Parkinson's disease.

Claims 62 and 63 appear to be free of the prior art of record because the prior art of record did not teach or suggest combining RPE and insulin-producing cells such as pancreatic islet of Langerhans cells as claimed.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 305-0196.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

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